Decreased Serum Brain-Derived Neurotrophic Factor May Indicate the Development of Poststroke Depression in Patients with Acute Ischemic Stroke: A Meta-Analysis

Hong-Bo Xu, PhD,*[,1] Yu-Hong Xu, MMed,†[,1] Ying He, BM,‡ Fang Xue, MMed,* Jing Wei, MMed,* Haigang Zhang, MMed,* and Jinglan Wu, MMed*

Background: Depression is a common complication after stroke and has been associated with poor outcome. Thus, it is of great importance to identify potential biomarkers that can aid in predicting and detecting patients with stroke at high risk of poststroke depression (PSD) development. Previous studies showed that brain-derived neurotrophic factor (BDNF) had potential use as a biomarker for discriminating patients with stroke at high risk of PSD. However, the results were inconsistent. *Methods:* A meta-analysis was performed to evaluate the correlation between the peripheral BDNF levels and the development of PSD in the acute stage of stroke. *Results:* Data were obtained from 4 studies including 499 patients with stroke. Among them, 171 patients were diagnosed with PSD at follow-ups. Our results showed that patients with stroke who were predisposed to developing PSD had significantly lower serum BDNF concentrations at the early stage of stroke. *Conclusions:* This study suggests a potential association between circulating BDNF concentrations at admission and subsequent PSD development, and provides additional support for the involvement of BDNF in the PSD development. **Key Words:** Poststroke depression—BDNF—biomarker—meta-analysis.

Introduction

Stroke is a common condition causing serious personal, family, and social burden. Stroke survivors are more predisposed to developing depression. A recent meta-analysis of 61 cohorts including 25,488 subjects showed that 31% of the patients suffered from depression at any time point up to 5 years after stroke.[1] Poststroke depression (PSD) not only significantly affects the quality of life of stroke survivors but also induces poor rehabilitation outcome and increases mortality and risk of stroke recurrence.[2,3] Accordingly, early identification and management of patients with stroke at high risk of developing PSD is important. However, it may be difficult to recognize PSD due to cognitive, language, and functional dysfunction in patients with stroke. Additionally, the pathogenesis of PSD remains unclear, and there are no objective methods for the diagnosis of PSD. Therefore, it may be of great significance to identify biomarkers present in the early stage of stroke that could aid in predicting and detecting patients who will develop PSD.[4]

Regarding the importance of brain-derived neurotrophic factor (BDNF) in the onset and development of depression,[5,6] previous studies have explored the correlation between peripheral BDNF level and the development of PSD in the acute period of stroke.[7-9] However, the results were inconsistent. The relationship between BDNF level

From the *Department of Critical Care Medicine, Nanshan People's Hospital, Shenzhen 518052, China; †Department of Pharmacy; and ‡Department of Laboratory Medicine, The Eighth Affiliated Hospital, Sun Yat-Sen University, Shenzhen 518033, China.

Received July 6, 2017; revision received September 26, 2017; accepted October 5, 2017.

Address correspondence to Hong-Bo Xu, PhD, Department of Critical Care Medicine, Nanshan People's Hospital, Shenzhen 518052, China. E-mail: xuhb1012@foxmail.com.; Address correspondence to Jinglan Wu, MMed, Department of Critical Care Medicine, Nanshan People's Hospital, Shenzhen 518052, China. E-mail: doctorwu99@126.com.

[1] These authors contributed equally to this work.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.10.003

and PSD development needs to be further evaluated. Hence, this meta-analysis was conducted to evaluate the association between BDNF level at the early stage of stroke and subsequent risk of PSD development, and provide evidence for the prevention of PSD.

Methods

This meta-analysis was performed according to the recommended guidelines of the Preferred Reporting Items of System Review and Meta-Analysis (PRISMA) statement.[10] Two reviewers (Y.H.X., Y.H.) independently performed the literature search and screening, data extraction, and quality assessment. Any disagreements were resolved through consensus, and a third reviewer (J.W.) was consulted if an agreement was not reached.

Data Sources and Searches

A comprehensive literature search was performed to identify relevant studies that reported the relationship between peripheral BDNF concentration at the early stage of stroke and subsequent PSD development. The following databases including Embase, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO (via EBSCO) were used to search the studies published in English. Additionally, we searched China Biology Medical (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang databases for publications in Chinese. Embase was first searched, and subsequent search strategies were derived from the Embase strategy and adapted for each database. The search strategy used in Embase was provided in the Supplementary material (Table S1). The retrieval time was limited from inception to April 27, 2017. The reference lists of the included studies were reviewed to avoid omitting relevant citations.

Study Selection

Studies satisfying the following criteria were included: (1) observational studies investigating the association between the plasma or serum BDNF level at the early stage of stroke and subsequent PSD development; (2) adult patients with stroke diagnosed clinically and imagistic (computed tomography or magnetic resonance imaging); (3) depression diagnosis after stroke as confirmed by either *Diagnostic and Statistical Manual of Mental Disorders* criteria or a validated rating scale for depression; (4) published in English or Chinese language. Studies were excluded by meeting one of the following criteria: (1) duplicated studies; (2) conference abstracts and dissertations; (3) review articles or case reports; (4) patients with a history of any concomitant psychiatric illnesses; (5) patient with severe concomitant physical disease or central nervous system disorders, such as Parkinson disease, brain tumors, and multiple sclerosis. (6) Data from the published results could not be extracted and analyzed.

Data Extraction and Quality Assessment

Data were extracted and recorded in a specially designed form, including key items for all eligible studies, such as first author, year of publication, sample size, gender, mean age, BDNF level, sample type, detection method, time interval between stroke onset and admission, sample collection time, follow-up duration, and method for depression diagnosis. For data that could not be directly retrieved, good faith efforts were applied to obtain the data by contacting the author through e-mails. The Newcastle–Ottawa scale criteria were used to assess the quality of each study.[11]

Data Synthesis

All the meta-analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The standard mean difference (SMD) was used to compare continuous variables. *P* values less than .05 were deemed statistically significant. All results were reported with 95% confidence intervals (CIs). If the mean or standard deviation of BDNF level could not be directly obtained from studies, we estimated the mean and deviation from the sample size, median, range, or interquartile range.[12,13] When data were presented in graphical form only, data values were estimated using the Engauge Digitizer.[14] The extracted data were included only if 2 reviewers independently had the same result.

Statistical heterogeneity between studies was assessed using the chi-square test with significance set at *P* value less than .10, and heterogeneity was quantified using the I^2 statistic. The random effect model was used to evaluate the pooled estimates. To explore the source of heterogeneity, sensitivity analysis was conducted to evaluate the key studies, which have substantial impact on the between-study heterogeneity according to the proposed algorithm.[15]

Results

The electronic literature search resulted in 633 references. According to the aforementioned criteria, 4 studies were pooled in this meta-analysis.[7-9,16] The flowchart of study selection is presented in Figure 1. Overall, a total of 499 patients with stroke were enrolled for follow-up, and 171 patients were diagnosed with PSD at follow-ups. The main characteristics of recruited studies are shown in Table 1. All studies were evaluated by Newcastle–Ottawa scale, and showed good qualities with a score of more than or equal to 6 stars.

Duo to the high heterogeneity ($P < .00001$, $I^2 = 96\%$), the random effect model was used. The result of meta-analysis demonstrated that serum levels of BDNF were